REMARKS

Status of the Claims

Claims 1-6 are pending in the application. Claim 1 has been amended to replace the transitional phrase "comprising" with the more limited scope transitional phrase "consists essentially of" with reference to the composition of the nucleic acid probes of the array. Each probe has the nucleic acid sequence of on of the sequences in the sequence listing. Applicants assert that no new matter is presented by these amendments and respectfully request entry of the same.

Objections

The specification was objected to for containing an embedded hyperlink. Applicants have amended the specification to remove the hyperlink.

Rejections under 35 U.S.C. § 101 should be withdrawn.

In paragraph 4, the Examiner has rejected claims 1-6 as allegedly lacking utility. The Examiner asserts that the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility. Applicants respectfully disagree. First, the Office Action alleges that the claimed invention lacks a "specific utility" because the disclosed uses of the nucleic-acids array of the mouse genome "are generally applicable to any nucleic acid."

Section 101 of Title 35 of the United States Code states that for an invention to be patentable it must be useful:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

Following the requirements of the Utility Examination Guidelines published at 66 FR 1092, Jan. 5, 2001, superseding the Revised Interim Utility Examination Guidelines that were published at 64 FR 71440, Dec. 21, 1999; 1231 O.G. 136 (2000); and correction at 65 FR 3425, Jan. 21, 2000; 1231 O.G. 67 (2000), a rejection based on lack of utility should not be imposed if the claimed invention has either a (1) well-established utility or the applicant has (2) asserted a specific and substantial utility that is credible. An assertion that the claimed invention is useful for a particular purpose is sufficient provided that the assertion would be considered credible by a person of ordinary skill in the art.

The claimed invention has a substantial utility:

In the utility guidelines training materials "substantial utility" is defined as "a utility that defined a 'real world' use". Several uses for the collection of probes are disclosed in the specification. For example, on page 17, lines 11-12, of the specification the following use for the arrays is disclosed: "simultaneous measurement of relative gene expression levels for at least 30,000 mouse genes."

This use defines a substantial real world use for the claimed invention. The claimed invention is not a single probe or probes to a single gene but probes to a collection of more than 30,000 mouse genes. Simply because the invention includes nucleic acid probes, the Examiner appears to require a demonstrated association between one of the genes and a "useful phenotype". Applicants respectfully assert that this is a misapplication of the utility guidelines and a misunderstanding of the claimed invention.

Applicant is not claiming a single probe to a single gene. What Applicant is claiming is an array of 982,914 twenty-five base probes to individually, reproducibly and accurately interrogate the expression level of a collection of more than 30,000 mouse genes and to do so

simultaneously. Each probe sequence is selected because they met specified criteria that allow them to function together in a single assay. Each probe is part of a probe set (typically 11 probes) that is designed to hybridize specifically to a known or predicted expression product from a mouse gene. The probes in the probe set are designed so that the probe set recognizes a particular target without cross hybridization to non-target transcripts that may be present in the sample. Probes are also selected for inclusion in a probe set so that they function together to give optimal performance under a specified set of hybridization conditions.

In particular, the commercial embodiment of the claimed invention, the GENECHIP Mouse 430 Array Set, has been used by researchers in studies to measure effects of specific treatments on gene expression in a mouse model. For example, in Black *et al., PNAS* 102(44):15948 (2005), a copy of which is provided herewith, researchers used the claimed array to identify gene expression patterns that differentiate the activities of transcription factors E2F1 and E2F3. The gene expression profiles were then used to confirm that specificity of E2F function is driven by the marked box domain present in the E3F protein, thus linking the biochemical mechanism proposed for E2F with the specificity observed in the gene expression signatures. The authors further indicate that "the ability to distinguish an E2F1- from an E2F3-expressing cell was facilitated by the ability to find patterns in the massive gene expression data that reflect subtle differences in the action of the two proteins." See Black *et al.* at p. 15953. The study also facilitated the identification of novel genes that are regulated by E2F.

In addition to this one example study, Applicants have also provided a selective list of additional peer reviewed publications describing studies performed using the Mouse 430

array set, see Appendix B. Applicants believe that the utilities asserted for the claimed invention are substantial and that this is demonstrated by the real world uses discussed above and demonstrated in these peer reviewed publications.

The claimed invention has a specific utility:

The training materials define a "specific utility" as "a utility that is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention." A utility need not be unique to a claimed invention and can be shared by a class of inventions. Ex parte Fisher at 1028. The outcome of this analysis depends on what the broad class of the invention should be. Applicants assert that the broad class for comparison should be all possible collections of 982,914 twenty-five base nucleic acids probes. There are 4^{25} different possible twenty-five base sequences so the number of possible combinations of 982,914 different twenty-five base probes is very large. Clearly not all possible sets of probes would have the asserted utility of the presently claimed set of probes. These probes are all perfectly complementary to mouse sequences and more specifically to mouse genes. Further, the probes are complementary to regions of the genome that are present in mouse mRNA and in particular the probes are complementary to the antisense RNA generated when mRNA is amplified by transcription amplification. Other sets of probes could be selected that would be complementary to and capable of measuring the level of a collection of messenger RNA from mice, but for any given message there are many different probes that could be selected. Not all sets of 982,914 probes would have the same utility as the claimed set of probes.

What Applicants are claiming is not an individual genomic sequence, but a collection of 982,914 genomic sequences that function as a set of probes to interrogate the expression

level of more than 30,000 mouse genes under selected amplification and hybridization conditions. The specification asserts a credible, substantial and specific utility for the claimed invention, making the rejection of the claims under 35 U.S.C. §101 improper.

Rejections under 35 U.S.C. § 112 should be withdrawn.

In paragraph 6, claims 1-6 are rejected under the first paragraph of 35 U.S.C. §112. The rejection of the claims under the enablement provision of 35 U.S.C. §112 is a corollary of the finding of lack of utility and Applicants request that it be reversed for the same reasons set forth in Applicants' arguments above regarding the rejection under 35 U.S.C. § 101.

In paragraph 7, claims 1-6 are rejected as failing to comply with the written description requirement. Claim 1 has been amended to replace the transitional phrase "comprising" with the more limited scope transitional phrase "consists essentially of" with reference to the composition of the nucleic acid probes of the array. The full length probes are no longer than 25 bases in length and have the sequence of one of the sequences in the sequence listing without additional flanking sequence. They may be attached to the array via a linker molecule.

Rejections under 35 U.S.C. § 102 should be withdrawn.

In paragraph 9, claims 1-5 are rejected as allegedly being anticipated by the Affymetrix Murine Genome U74 Set, version 2 (Mar 2001). Applicants respectfully traverse this rejection. The collection of probes present on the Affymetrix Murine Genome U74 array set is not identical to the collection of probes of the claimed array. The majority of the sequences of the probes on the presently claimed array are different from the probes of the U74v2 array. In addition, the presently claimed array includes approximately 300,000 more probes than the U74v2 array (982,914 vs. ~650,887).

Applicants provied the following example to demonstrate that the probes of the presently claimed array differ in sequence from the probes of the U74v2 array set. Presently claimed SEQ ID NO 1 (5'aaaaaaaaat cacggccagg catgg 3') was used as a starting point. This probe corresponds to one probe from a probe set on the array for detection of expression products from the gene Ddx42. The presently claimed array contains two probe sets to detect this gene. The 11 probes in the first probe set are as follows:

SEQ ID NO 1	AAAAAAAAAT CACGGCCAGG CATGG
SEQ ID NO 135309	ACTTGAAGTA CTCCTTCATG CTTCC
SEQ ID NO 396605	CTTGAAGTAC TCCTTCATGC TTCCT
SEQ ID NO 931959	TTCATGCTTC CTCCTCCAAA TAGCT
SEQ ID NO 262263	ATGCTTCCTC CTCCAAATAG CTGGG
SEQ ID NO 876225	TGCTTCCTCC TCCAAATAGC TGGGA
SEQ ID NO 632095	GGGATTATGG GTTCATGCCA CCAGG
SEQ ID NO 606716	GGATTATGGG TTCATGCCAC CAGGC
SEQ ID NO 520070	GATTATGGGT TCATGCCACC AGGCC
SEQ ID NO 277618	ATTATGGGTT CATGCCACCA GGCCC
SEQ ID NO 926450	TTATGGGTTC ATGCCACCAG GCCCA

The second probe set for Ddx42 on the presently claimed array has the following 11 probes:

SEQ ID NO 381290	CTGAGCTGGC CCTGGAAAGC AGAGA
SEQ ID NO 182160	AGCTGGGAAG CTTTTGTTTG TTGTG
SEQ ID NO 198929	AGGGCACAAA AACTCACTCT AGGTT
SEQ ID NO 982030	TTTTTCTTAG CTGTGGCCAG GCAGT
SEQ ID NO 652941	GGTGCTTTCA GATGTTTGCA GGGAA
SEQ ID NO 863960	TGCAGGGAAG ATGCCTGAGC GCTCA
SEQ ID NO 339506	***CCAGCCCTGA GACACGTAGG AAAGA***
SEQ ID NO 438527	GAATGATCAT CTTGGAAGGA TTCCA
SEQ ID NO 59195	AAGGATTCCA GGATAATCCA GGCCT
SEQ ID NO 242517	ATCCAGGCCT GGAGTACTGC TAAAT
SEQ ID NO 743904	TAAAACCAAC CCCAACAGTA GCATT

The probe set for Ddx42 in the Affymetrix Murine Genome U74v2 array set contains the following 16 probes:

	CAGTCCCAAC TTCTGCCCTG TTAGG
	CAACTTCTGC CCTGTTAGGG ATGCT
	TTCTGCCCTG TTAGGGATGC TTGGG
	AGCAGTGGTG CTTTCAGATG TTTGC
	TTCAGATGTT TGCAGGGAAG ATGCC
	CAGACTGTTT CCAGCCCTGA GACAC
SEQ ID NO 339506	***CCAGCCCTGA GACACGTAGG AAAGA***

GCTTTGAAAT CCTAAGCCAT TAGGA
TTTGAAATCC TAAGCCATTA GGACT
ATCCTAAGCC ATTAGGACTG AAGGA
AATGATCATC TTGGAAGGAT TCCAG
CATCTTGGAA GGATTCCAGG ATAAT
ATTCCAGGAT AATCCAGGCC TGGAG
TCCAGGCCTG GAGTACTGCT AAATT
GCCTGGAGTA CTGCTAAATT TACCA
AACCCCAACA GTAGCATTCA AAGTG

The only probe in the Ddx42 probe sets that is present on both the presently claimed array and the U74v2 array is SEQ ID NO 339506. The remaining 15 probes from the Ddx42 probe set on the U74v2 array are not on the presently claimed array and the remaining 21 probes from the presently claimed array are not on the U74v2 array. Looking at just this one gene there are 21 probes that are on the presently claimed array but not on the U74v2 array.

Differences in the two arrays reflect that the U74v2 array was designed using Build 74 of the UniGene database, while the presently claimed array was designed using Build 107 of the UniGene database combined with the Mouse Genome from the Whitehead Institute Center for Genome Research (MGSC, April 2002). These two sources represent different target content for probe design. The presently claimed array also includes differences resulting from improvements in probe design methods and in software analysis methods, for example, the U74v2 array uses 16 perfect match probes per probe set while the presently claimed array uses only 11. The presently claimed array also targets increased content, with the presently claimed array including approximately 45,000 probe sets compared to approximately 36,000 for the U74v2 array. The density of the probes on the 430 array is also higher than the U74v2, allowing for approximated 300,000 additional 25 base probes on the 430 array compared to the U74v2 array (982,914 vs. ~650,887). The U74v2 array therefore fails to teach each and every limitation of the present claims.

Rejections under 35 U.S.C. § 103 should be withdrawn.

In paragraph 12, claim 6 is rejected over the Affymetrix Murine Genome U74v2 Set, version 2 (March, 2001) in view of Fodor et al. (US Pat 6,309,822). Claim 6 is directed to an array as disclosed in claim 1 with the added limitation that the array is a single contiguous solid support. As the Examiner has noted, the U74v2 set is a 3 array set with the probes being separated onto 3 non-contiguous chips.

To establish a *prima facie* case of obviousness the prior art reference or references must teach or suggest all the claim limitations. Neither the U74v2 array nor Fodor et al. teach or suggest the specific set of probes claimed in independent claim 1. As discussed above, the claimed set of probes does not significantly overlap the set of probes on the U74v2 in sequence and there are at least 300,000 probes that are present on the claimed array that are not present on the U74v2 array. Therefore, the Examiner has failed to establish a *prima facie* case of obviousness.

In paragraph 13, claims 1-6 are rejected over Unigene build 107 (June 2002) in view of Fodor et al., (US Pat 6,309,822). The Unigene database is cited as teaching the sequences of mouse genes and ESTs and, as indicated in the specification, the claimed probe sequences are complementary to genes and EST clusters from this build of the database. Fodor et al. is cited as teaching that arrays may comprise up to 1,000,000 different oligonucleotide probes that are preferably 20 to 25 nucleotides in length. The Examiner is of the opinion that, given the sequence information provided in Unigene build 107 and the information provided in Fodor about the length and number of probes, it would have been obvious to select the particular 982,914 sequences claimed. From this it would appear to follow that any set of twenty-five base probes targeting the transcripts of Unigene build 107 would be equivalent to

the selected set of probes. Applicants respectfully disagree. The 982,914 probes selected for inclusion in the array are a unique set of probes that were carefully selected to function as a set on an array for gene expression analysis. The choice of probe sequence depends on numerous criteria, such as hybridization behavior, secondary structure, propensity for cross hybridization to other probes in the set, target preparation methods and manufacturing considerations. Not all sets of 982,914 twenty-five base probes from Unigene build 107 would have the function of the claimed set. There are likely other sets of probes that could have been selected to have similar function, but the specific claimed set of probes was chosen from the many possible sets of probes to obtain an array that has optimal performance given our current understanding of probe, array and assay performance.

In paragraph 14, claims 1-6 are rejected over Unigene build 74 in view of Fodor et al. (US Patent 6,309,822). As discussed above, Fodor et al. in combination with Unigene build 107 fails to anticipate the presently claimed specific set of probes. Unigene build 74 contains at best a subset of the information contained in Unigene build 74 and the combination of Unigene build 74 with Fodor et al. fails to make the presently claimed invention obvious for at least the same reasons.

In paragraph 15, claims 1-6 are rejected over Marshall (Science, vol. 296, May 10, 2002; p. 1005) in view of Fodor. Marshall is cited as teaching the completion of 96% of the sequence of the mouse genome. As discussed above, Fodor et al. in combination with Unigene build 107 fails to anticipate the presently claimed specific set of probes. A database as taught by Marshall that contains 96% of the complete mouse genome contains more sequence information but less annotation information about which regions of the genome contain genes. It would be even less likely that one of skill in the art would identify a set of

probes that are equivalent in function to the claimed set of probes by combining Marshall with Fodor et al. Therefore the combination of Marshall and Fodor et al. fails to make the presently claimed invention obvious for at least the same reasons.

In paragraph 16, claims 1-6 are rejected over Marshall II (Marshall, Science, vol. 292, May 4, 2001; p.822) in view of Fodor. Marshall II is cited as teaching the completion of the draft of the sequence of the mouse genome. The citation does not teach any sequence and simply reports on the claimed progress of two competing groups attempting to sequence the mouse genome. According to Marshall II, the public group, the Mouse Sequencing Consortium (MSC) at the time was making available sequences that were typically less than 500 bases, which is much shorter than a typically gene, and had a genome that was ~90% complete. This information would be difficult to use as a basis for design of probes to expressed regions of genes as presently claimed. The second group, Celera Genomics, had reported a more comprehensive mouse genome with ~99% coverage, available to subscribers. Again, there is no indication that the Celera database contained information about which regions of the genome were expressed and which were not. As discussed above, the presently claimed invention is not obvious over a genome database containing gene annotation information (Unigene build 107) in view of Fodor et al. For at least the same reasons, the presently claimed invention is not obvious over a non-annotated and incomplete genome database in view of Fodor et al.

CONCLUSION

For these reasons, Applicants believe all pending claims are now in condition for allowance. If the Examiner has any questions pertaining to this application or feels that a telephone conference would in any way expedite the prosecution of the application, please do not hesitate to call the undersigned at (408) 731-5000.

Respectfully submitted,

/Sandra E. Wells/
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Date: August 31, 2006

Attachments: Appendix A: List of Publications
Black et al. 2005

Customer No.: 22886
Legal Department
Affymetrix, Inc.
3420 Central Expressway
Santa Clara, CA 95051
Tel: 408/731-5000
Fax: 408/731-5392

APPENDIX A

1. **Disruption of the cingulin gene does not prevent tight junction formation but alters gene expression.**
Guillemot, L. *et al.* Journal of Cell Science 117, 5245-56jcs.01399, 2004.

2. **Foxa2 is required for transition to air breathing at birth.**
Wan, H. *et al.* Proceedings of the National Academy of Sciences 101(40), 14449-54, 2004.

3. **Distinct ontogenic and regional expressions of newly identified Cajal-Retzius cell-specific genes during neocorticogenesis.**
Yamazaki, H. *et al.* Proceedings of the National Academy of Sciences 101(40), 14509-14, 2004.

4. **The PP2A-associated protein {alpha}4 is an essential inhibitor of apoptosis.**
Kong, Mei *et al.* Science 306(5696), 695-698, 2004.

5. **A target selection of somatic hypermutations is regulated similarly between T and B cells upon activation-induced cytidine deaminase expression.**
Kotani, A. *et al.* Proceedings of the National Academy of Sciences 102(12), 4506-11, 2005.

6. **Two types of precursor cells in a multipotential hematopoietic cell line.**
Ye, Z. J. *et al.* Proceedings of the National Academy of Sciences of the United States of America 102(51), 18461-6, 2005.

7. **Transcriptional and behavioral interaction between 22q11.2 orthologs modulates schizophrenia-related phenotypes in mice.**
Paterlini, M. *et al.* Nature Neuroscience 8(11), 1586-94, 2005.

8. **PPARdelta regulates glucose metabolism and insulin sensitivity.**
Lee, C. H. *et al.* Proceedings of the National Academy of Sciences of the United States of America 103(9), 3444-9, 2006.

9. **Targeting of GFP to newborn rods by Nrl promoter and temporal expression profiling of flow-sorted photoreceptors.**
Akimoto, M. *et al.* Proceedings of the National Academy of Sciences of the United States of America 103(10), 3890-5, 2006.

10. **PKBalpha is required for adipose differentiation of mouse embryonic fibroblasts.**
Baudry, A. *et al.* Journal of Cell Science 119(5), 889-97, 2006.

11. **Nogo-A-deficient mice reveal strain-dependent differences in axonal regeneration.**
Dimou, L. *et al.* Journal of Neuroscience 26(21), 5591-603, 2006.

12. **Insulin-like growth factors 1 and 2 induce lymphangiogenesis in vivo.**
Bjoerndahl, M. *et al.* Proceedings of the National Academy of Sciences of the United States of America 102(43), 15593-8, 2005.

13. **Zfp312 is required for subcortical axonal projections and dendritic morphology of deep-layer pyramidal neurons of the cerebral cortex.**
Chen, J. G. *et al.* Proceedings of the National Academy of Sciences of the United States of America 102(49), 17792-7, 2005.

14. **Inactivation of the Snf5 tumor suppressor stimulates cell cycle progression and cooperates with p53 loss in oncogenic transformation.**
Isakoff, M. S. *et al.* Proceedings of the National Academy of Sciences of the United States of America 102(49), 17745-50, 2005.

15. **Androgens regulate the permeability of the blood-testis barrier.**
Meng, J. *et al.* Proceedings of the National Academy of Sciences of the United States of America 102(46), 16696-700, 2005.

16. **Evolutionary regulation of the blind subterranean mole rat, Spalax, revealed by genome-wide gene expression.**
Brodsky, L. I. *et al.* Proceedings of the National Academy of Sciences of the United States of America 102(47), 17047-52, 2005.